Please add the following paragraph at page 66, after line 11:

Fig. 29 illustrates the structures of amonafide and N-acetylamonafide according to another embodiment of the present invention;

Please replace the paragraph at page 66, lines 12 through 14 with the following paragraph:

Fig. 30 illustrates a nomogram for the determination of body surface area in accordance with yet another embodiment of the present invention.

Please replace the paragraph at page 67, line 19 through page 68, line 8 with the following paragraph:

Accordingly, the present invention will be exemplified in accordance with methods of determining phenotypic determinants for NAT2. The determination of metabolic determinants for NAT2 may be performed as a single determination or in combination with methods of determining a phenotypic profile for any other drug metabolizing enzymes including at least one of the following enzymes: NAT1, CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A4, CYP2C9 and CYP2C19, UGT, GST, ST. The metabolites of suitable probe substrates for some of these enzymes are illustrated in Figs. 2-10. These enzymes are involved in the metabolism of a large number of drugs, and as a result have important implications in the outcome of individual drug treatment regimes, and hence, clinical trial studies. These enzymes and their corresponding phenotypic determinants as described herein are provided as a representative example of determinants for the purposes of exemplifying the multi-determinant metabolic phenotyping of the present invention. However, the present invention is not limited thereto.

Please replace the paragraph at page 78, lines 2 through 14 with the following paragraph:

Different probe substrates can be used to determine the NAT2 phenotype. In accordance with the present invention a suitable probe substrate is, without limitation caffeine. Caffeine is widely consumed and relatively safe. A phenotype may be generally determined from ratios of the caffeine metabolites 5-acetamino-6-amino-1-methyluracil (AAMU) or 5-acetamino-6-formylamino-1-methyluracil (AFMU) and 1-methylxanthine (1X) present in urine samples of an individual collected after drinking coffee. The structures of these metabolites are illustrated in Fig. 2. The ratio of these metabolites provides a determination of an individual's N-acetylation (NAT2) phenotype.

Please replace the paragraph at page 85, lines 17 through 25 with the following paragraph:

Of these midazolam is the preferred probe substrate. The structures of midazolam and its hydoxylated metabolite, 1'-hydroxymidazolam are illustrated in Fig. 4. In accordance with the present invention, the molar ratio of midazolam and its metabolite is used to determine the CYP3A4 phenotype of the individual as follows:

$$\frac{\text{1'-hydroxymidazolam}}{\text{midazolam}}$$

Please replace the paragraph at page 88, lines 15 through 17 with the following paragraph:

Of these pASA is the preferred probe substrate. The structure

of pASA and its acetylated metabolite p-acetylaminosalicylic acid are illustrated in Fig. 5.

Please replace the paragraph at page 91, lines 7 through 12 with the following paragraph:

A probe substrate can be used to determine the CYP2A6 phenotype (coumarin). In accordance with the present invention suitable probe substrates include, without limitation, coumarin. The structure of coumarin and its metabolite 7-hydroxycoumarin are illustrated in Fig. 6.

Please replace the paragraph at page 94, lines 24 through page 95, line 6 with the following paragraph:

In accordance with an embodiment of the present invention, the ratio of S-(+)mephenytoin and R-(-)mephenytoin in an urine sample may be used to provide a determination of an individual's CYP2C19 phenotype. These metabolites are used as quantitative markers in the determination of a CYP2C19 phenotype on the basis of the use of the preferred probe substrate mephenytoin. However, it is fully contemplated that the present invention is not limited in any respect thereto.The structure of R-(-) and S-(+) mephenytoin and 4-hydroxymephenytoin are illustrated in Fig. 7.

Please replace the paragraph at page 98, line 27 through page 99, line 12 with the following paragraph:

In accordance with an embodiment of the present invention, the ratio of (S)-ibuprofen and its carboxylated metabolite, (S)-2-carboxyibuprofen in a urine sample may be used to provide a determination of an individual's CYP2C9 phenotype. These

metabolites are used as quantitative markers in the determination of a CYP2C9 phenotype on the basis of the use of the preferred probe substrate (S)-ibuprofen. The structures of (S)-ibuprofen and its metabolite (S)-2-carboxyibuprofen are illustrated in Fig. 8. However, it is fully contemplated that the present invention is not limited in any respect thereto. In fact, due to the nature of the substrate specific alterations caused by the individual CYP2C9 mutations, multiple probe substrates may be necessary for a completely informative phenotypic determination of CYP2C9.

Please replace the paragraph at page 105, lines 3 through 6 with the following paragraph:

Of these dextromethorphan is the preferred probe substrate. The structure of dextromethorphan and its demethylated metabolite dextrorphan are illustrated in Fig. 9.

Please replace the paragraph at page 109, lines 23 through 24 with the following paragraph:

The structures of chlorzoxazone and its metabolite 6-hydroxychlorzoxazone are illustrated in Fig. 10.

Please replace the paragraph at page 113, lines 6 through 15 with the following paragraph:

The metabolic phenotype can be determined directly (by measuring enzyme activity) or indirectly (by examining enzymes genetic sequence). In general, for example, for direct phenotyping, a probe substrate or substrates, such as those exemplified in Table 1 are administered to an individual to be

phenotyped. A biological sample, such as a urine sample is subsequently collected from the individual approximately 4 hours after administering the probe substrate(s). The urine sample is analyzed according to a ligand binding assay, such as enzyme-linked immunosorbent assay (ELISA) technology as described hereinbelow, for metabolites corresponding to the probe substrate(s) and the molar ratios of the metabolites calculated to reveal the individual phenotypes.

Please replace the paragraph at page 125, line 25 through page 126, line 6 with the following paragraph:

The general immunosensor design is depicted in Fig. 11. There are four types of immunosensor detection devices: electrochemical (potentiometric, amperometric or conductometric/capacitative), optical, microgravimetric, and thermometric. All types can either be run as direct nonlabeled or as indirect labeled immunosensors. The direct sensors are able to detect the physical changes during the immune complex formation, whereas the indirect sensors use signal-generating labels which allow more sensitive and versatile detection modes when incorporated into the complex.

Please replace the paragraph at page 138, lines 4 through page 139, line 14 with the following paragraph:

The general principle of SPR measurement 80 is depicted in Fig. 12. Polarized light is directed from a layer of high RI towards a layer with low RI to result in total internal reflection. The sample is attached to the layer of low RI. At the interface between the two different media, a thin approximately 50 nm gold film is interposed. Although light does not propagate into the low

RI medium, the interfacial intensity is not equal to zero. The physical requirement of continuity across the interface is the reason for exciting the surface electrons "plasmons" in the metal film by the light energy. As a result, the electrons start oscillating. This produces an exponentially decaying evanescent wave penetrating a defined distance into the low RI medium, which is accountable for a characteristic decrease in the intensity of the reflected light. Hence, a direct insight in changes of the RI at the surface interface is made possible by monitoring the intensity and the resonance angle of the reflected light, caused by the biospecific interactions which took place there. Whereas in the BIAcore™ system, the light affects the sensing layer only once, there are several propagation contacts in the IAsys™ due to the device's resonant mirror configuration. The BIAcore™ SPR apparatus is characterized by a sensitive measurement of changes of the RI when polarized laser light is reflected at the carboxy-methylated dextranactivated device interface. The IAsys™ SPR device also uses a carboxy-methylated dextran-activated surface. Its dextran layer, however, is not attached to a gold surface, but to titanium, which forms a high refractive dielectric resonant layer. The glass prism is not attached tightly on the opposite side of the titanium layer, making space for an interposed silica layer of low RI. By this layer, the laser light beam couples into the resonant layer via the evanescent field. Therefore, the IAsys™ is seen as a combination of SPR resonant mirror with waveguide technology. As a result, no decrease in the reflected light intensity at resonance is observed in this system. The specific signal is the change in the phase of the reflected polarized light.

Please replace the paragraph at page 141, line 22 through page 142, line 12 with the following paragraph:

The TSM sensor consists of an AT-cut piezoelectric crystal disc, most commonly of quartz because of its chemical stability in biological fluids and resistance to extreme temperatures. The disc is attached to two metal electrodes on opposite sides for the application of the oscillating electric field. The TSM is run in a range of 5-20 MHz. The schematic design of a typical TSM device shown in Fig. 13. Advantages are, besides the chemical inertness, the low cost of the devices and the reliable quality of the mass-produced quartz discs. Major drawbacks of the system are the insensitivity for analytes with a molecular weight -1000 Da, and, as seen in all label-free immunosensor systems, nonspecific binding interferences. Nonspecific binding effects are hard to distinguish from authentic binding events due to the fact that no reference line can be placed in the sensor device. For a SH-APM device, however, by appropriately selecting the device frequency, these spurious responses can be suppressed. This sensor is applicable for measurements in human serum matrix.

Please replace the table at page 143 with the following table:

Table 1

Examples of Enzymes and Corresponding Probes Drugs

Enzyme	Probe substrate
NAT1	p-aminosalicylic acid
NAT2	Caffeine
CYP1A2	Caffeine
CYP2A6	Coumarin
CYP2C9	s-ibuprofen
CYP2C19	Mephenytoin
CYP2D6	Dextromethorphan
CYP2E1	Chlorzoxazone
CYP3A4	Midazolam

Please replace the paragraph at page 147, lines 1 through line 3 with the following paragraph:

The synthetic route for the production of AAMU-hemisuccinic acid (VIII) and 1-methylxanthine-8-propionic acid (IX) is presented in Fig. 14.

Please replace the paragraph at page 150, lines 26 through line 29 with the following paragraph:

The derivatives shown in Figs. 15 and 16 can also be used for raising antibodies against AAMU or AFMU that can be used for

measuring the concentrations of these caffeine metabolites in urine samples.

Please replace the paragraph at page 151, lines 19 through 22 with the following paragraph:

The other derivatives of 1X, shown in Figs. 17 and 18, can also be used for raising antibodies against 1X and thereby to allow the development of an ELISA for measuring 1X concentration in urine samples.

Please replace the paragraph at page 164, line 16 through page 165, line 3 with the following paragraph:

The competitive antigen ELISA curves of AAMU-Ab and 1X-Ab determinations obtained in duplicate are presented in Fig. 19. Each calibration curve represents the average of two calibration curves. The height of the bars measure the deviations of the absorbency values between the two calibration curves. Data points without bars indicate that deviations of the absorbency values are equal or less than the size of the symbols representing the data points. Under the experimental conditions of the ELISA: background was less than 0.10 au; the practical limits of detection of AAMU and 1X were 2 x 10-7 M and 2 x 10-6 M, respectively, concentrations 500 and 50 times lower than those in urine samples from previous phenotyping studies (Kilbane, A.J. et al. (1990) Clin. Pharmacol. Ther., 47:470-477); the intra-assay and interassay coefficients of variations of AAMU and 1X were 15-20% over the concentration range of 0.01-0.05 mM.

Please replace the paragraph at page 165, lines 17 through 23 with the following paragraph:

The cross reactivities of AAMU-Ab and 1X-Ab were tested using a wide variety of caffeine metabolites and structural analogs (Table 2 below). AAMU-Ab appeared highly specific for binding AAMU, while 1X-Ab appeared relatively specific for binding 1X. However, a 11% cross reactivity was observed with 1-methyluric acid (1U), a major caffeine metabolite.

Please replace the title of the table at page 166, lines 3 through 5 with the following title:

Table 2

Cross-reactivity of AAMU-Ab and 1X-Ab towards different caffeine metabolites and structural analogs

Please replace the paragraph at page 166, line 16 through page 167, line 9 with the following paragraph:

The relative high level of cross reactivity of 1U is, however, unlikely to interfere significantly in the determination of 1X and the assignment of NAT2 phenotypes, since the ratio of 1U:1X is no greater than 2.5:1 in 97% of the population (Tang, B-K. et al. (1991) Clin. Pharmacol. Ther., 49:648-657). This is confirmed by measurements of apparent concentrations of 1X when the ratio varied between 0-8.0 at the fixed 1X concentration of 3 x 10-6 M (Table 3 below). At 1U:1X ratios of 2.5 and 3.0, the apparent increases were 22% and 32%, respectively.

Please replace the title of the table at page 167, lines 11 through 14 with the following title:

Table 3

The effect of the ratio 1U:1X on the determination of 1X concentration by ELISA at fixed 1X concentration

of 3 x 10^{-6} M

Please replace the paragraph at page 168, lines 17 through 29 with the following paragraph:

3) The ELISA was used in determining the NAT2 phenotype distribution within a group of 146 individuals. Fig. 20 illustrates a histogram of the NAT2 phenotypes of this group as determined by measuring the AAMU/1X ratio in urine samples by ELISA. Assuming an antimode of 1.80, the test population contained 60.4% slow acetylators and 39.6% fast acetylators. This is consistent with previously reported distributions (Kalow, W. et al. (1993) Clin. Pharmacol. Ther., 53:503-514; Kilbane, A.J. et al. (1990) Clin. Pharmacol. Ther., 47:470-477).

Please replace the title of the table at page 169, lines 6 through 8 with the following title:

Table 4

Content of the ELISA kit and conditions of storage

Please replace the title of the table at page 171, line 1 with the following title:

Table 5

Please replace the paragraph at page 171, lines 33 through page 172, line 13 with the following paragraph:

Prepare Table 6 with a computer and print it. This table shows the content of each well of a 96-well microtiter plate. Enter the name of the urine sample (or number) at the corresponding well positions in Table 6. Select the dilution factor (D.F.) of each urine sample and enter at the corresponding position in Table 6. Enter the dilution of each urine sample with buffer B at the corresponding position in Table 6: for example, for a D.F. of 100 (100 mL of 10x diluted urine sample + 900 mL buffer B), enter 100/900. See "Dilutions of urine samples..." procedure described above for the preparation of the different dilutions. Prepare the different dilutions of the urine samples in 1.5-mL microtubes. Prepare Table 7 with a computer and print it. Prepare the following 48 microtubes in the order indicated in Table 7.

Please replace the title of the table at page 173, lines 1 through 3 with the following title:

Table 6

Positions of blanks, control and urine samples in a microtiter plate

Please replace the title of the table at page 174, lines 1 through 3 with the following title:

Table 7

Content of the different microtubes

Please replace the title of the table at page 176, lines 2 through 5 with the following title:

Table 8

Standard solutions of AAMU and 1X (diluted with buffer B)

Please replace the paragraph at page 176, line 26 through page 177, line 7 with the following paragraph:

Add 50 mL/well of AAMU-HRP (or 1X-HRP) conjugate solution, starting from the last row. Add 50 mL/well of diluted urine samples in duplicate, standards, blank with a micropipet (0-200 mL), starting from well # 96 (see Table 6). Cover the plate and mix gently by vortexing for several seconds. Leave the plate at room temperature for 3 h. Wash 3 times with 100 mL/well with buffer C, using a microtiter plate washer. Wash 3 times with 100 mL/well with the 0.05% Tween™ 20 solution. Add 150 mL/well of Buffer E-H2O2 (prepared just prior adding to the microtiter plate wells). Shake 20-30 min at room temperature with an orbital shaker. Add 50 mL/well of a 2.5 N HCl solution. Shake 3 min with the orbital shaker at room temperature. Read the absorbance of the wells with microtiter plate reader at 490 nm. Print the sheet of data and properly identify the data sheet.

Please replace the paragraph at page 177, lines 11 through 22 with the following paragraph:

Draw a Table 9 with a computer. Using the data sheet of the microtiter plate reader, enter the average absorbance values of blanks, controls (no free hapten present), standards and samples in Table 9. Draw the calibration curve on a semi-logarithmic plot (absorbance at 490 nm as a function of the standard concentrations) using sigma plot (or other plot software). Find the [AAMU] (or [1X]) in the microtiter well of the unknown from the calibration curve and enter the data in Table 10. Multiply the [AAMU] (or [1X]) of the unknown by the dilution factor and enter the result in the corresponding case of Table 10.

Please replace the title of the table at page 178, lines 1 through 2 with the following title:

Table 9

Average absorbance values of samples in the microtiter plate

Please replace the title of the table at page 179, lines 1 through 2 with the following title:

Table 10

AAMU (or 1X) concentrations in urine samples

Please replace the title of the table at page 180, lines 1 through 2 with the following title:

Table 11

Composition of the different buffer

Please replace the paragraph at page 184, lines 6 through 8 with the following paragraph:

The synthetic routes for the production of caffeine, 1,7-dimethylxanthine, 1,7-dimethyluric acid derivatives are shown in Figs. 21 and 22.

Please replace the paragraph at page 195, line 9 through page 197, line 12 with the following paragraph:

Buffers and water without additives are filtered through 0.45 µM millipore filters and kept for one week, except the substrate buffer which is freshly prepared. BSA, antibodies, Tween™ 20 and horse radish peroxidase are added to buffers and water just prior to use. Urine samples are usually collected four hours after drinking a cup of coffee (instant or brewed with approximately 100 mg of caffeine per cup) and stored at -20°C as 1-mL aliquots in 1.5-mL microtubes. For the ELISA, the urine samples are diluted with isotonic sodium phosphate buffer, pH 7.5 (310 mosM) to give concentrations of caffeine, 1.7-DMX and 1,7-DMU no higher than 3 x 10^{-6} M in the microtiter plate wells. Wells of the ELISA plate are washed with a Nuc-Immuno wash 12 washer. Sixteen milliliters of a solution of 6.6 $\mu g\ ml^{-1}$ of isolated IgG antibodies is prepared in a 100 mM sodium carbonate buffer, pH 9.6, and 150 µL of this solution is pipetted in each well of a microtiter plate using a eight channel pipet (Brinkmann Transferpette™-8 50-200 µL) and 200 µL Flex tips from Brinkmann). After coating the wells with antibodies at 4°C for 20 hours, the wells are washed 3 times with the isotonic sodium phosphate buffer containing 0.05% Tween™ 20 (IPBT) and properly drained by inverting the plate and absorbing the liquid on to a piece of paper towel. Thirty milliliters of a solution of a IPBT solution containing 1% BSA is prepared and 150 µL of this solution is pipetted in each well using a eight channel pipet (Brinkmann Transferpette™-8 50-200 µL) and 200 µL yellow tips

(Sarstedt yellow tips for P200 Gilson Pipetman). After 3 hours at room temperature, the wells are washed 3 times with IPBT solution and drained. Samples of 400 µL for determination of caffeine, 1,7-DMX and 1,7-DMU are prepared in 1.5-mL microtubes using Sarstedt yellow tips and a P200 Gilson Pipetman. Then, 200 µL of each sample are pipetted in duplicate in a Falcon 96-well microtest tissue culture plate according to the pattern shown in Figure 23, using Sarstedt yellow tips and a P200 Gilson Pipetman. Using an eight channel pipet (Brinkmann Transferpette™-8 50-200 µL) and changing the tips of the eight channel pipet (200µL Flex tips from Brinkmann) at each row, 150 µL of samples are transferred in the corresponding wells of a 96-well ELISA microtiter plate coated with antibodies. After the addition of the samples, the microtiter plates are covered and left standing at room temperature for 2h. While the plate is left standing the substrate buffer without the hydrogen peroxide and o-phenylenediamine hydrochloride is prepared (25 mM citric acid and 50 mM sodium phosphate dibasic buffer, pH 5.0). The microtiter plate is washed 3 times with the IPBT solution and 3 times with a 0.05% Tween™ 20 solution and drained. Then, 50 µL of hydrogen peroxide and 40 mg of o-phenylenediamine are added to the substrate buffer. One hundred fifty microliters (150 µL) of the substrate buffer solution is then added to each well using a eight channel pipet (Brinkmann Transferpette™-8 50-200 µL) and 200µL Flex tips (Brinkmann). The microtiter plate is covered and shaken for 25-30 min at room temperature and the enzymatic reaction is stopped by adding 50 µL/well of a 2.5 N Hcl solution using an eight channel pipet (Brinkmann Transferpette™-8 50-200 µL) and 200µL Flex tips (Brinkmann). After gently shaking for 3 min., the absorbance is read at 490 nm with a microplate reader.

Please replace the paragraph at page 197, lines 24-25 with the following paragraph:

The standard solutions of the above compounds are prepared as outlined in Table 12 below.

Please replace the title of the table at page 198, lines 1 and 2 with the following title:

TABLE 12

Standard Solutions

Please replace the paragraph at page 199, lines 3-10 with the following paragraph:

To ensure accuracy in the ELISA measurement of CYP1A2 phenotyping, the antibodies must have specificity for their individual caffeine metabolites, with little or no recognition of other derivatives. To ensure their selectivity an ELISA is performed with standard solutions of the compounds listed in Table 13. An ideal antibody specificity result is hypothesized with the Table 13 as well.

Please replace the title of the table at page 200, lines 1 through 3 with the following title:

Table 13

Cross-reactivity of caffeine-Ab, 1,7-DMX-Ab and 1,7-DMU-Ab towards caffeine metabolites and structural analogs

Please replace the title of the table at page 202, lines 7 through 9 with the following title:

Table 14

Content of the ELISA kit and conditions of storage

Please replace the title of the table at page 203, line 9 with the following title:

Table 15

Please replace the paragraph at page 204, lines 5-21 with the following paragraph:

Prepare Table 16 with a computer and print it. This table shows the contents of each well of a 96 well microtiter plate. Enter the name of the urine sample (or number) at the corresponding well positions in Table 16. Select the dilution factor (D.F.) of each urine sample and enter at the corresponding position in Table 16. Enter the dilution of each urine sample with buffer B at the corresponding position in Table 16: for example a D.F. of 100 (100μL of 10x diluted urine sample + 900 μL buffer B), enter 100/900. See "Dilutions of urine samples..." procedure described above for the preparation of the different dilutions. Prepare the different dilutions of the urine samples in 1.5 mL microtubes using a styrofoam support for 100 microtubes. Prepare Table 17 with a computer and print it. Using a styrofoam support (100 microtubes), prepare the following 48 microtubes in the order indicated in Table 17.

Please replace the title of the table at page 205, lines 1 through 2 with the following title:

Table 16

Positions of blanks, control and urine samples in a microtiter plate

Please replace the title of the table at page 206, lines 1 through 2 with the following title:

Table 17

Content of the different microtubes

Please replace the title of the table at page 208, lines 1 through 2 with the following title:

Table 18

Standard solutions of caffeine, 1,7-DMX and 1,7-DMU (diluted with buffer B)

Please replace the paragraph at page 208, line 5 through page 209, line 7 with the following paragraph:

Add 50 µL/well of Caffeine-HRP (1,7-DMX-HRP or 1,7-DMU-HRP) conjugate solution starting from the last row. Add 50 µL/well of diluted urine samples in duplicate, standards, blank with a micropipet (0-200 µL), starting from well #96 (see Table 19). The plate is covered and mixed gently by vortexing for several seconds. The plate is left at room temperature for 3 hours. The plate is then washed three times with 100 µL/well buffer C, using a microtiter plate washer. The plate is then washed 3 times with 100 µL/well 0.05% Tween™ 20 solution. Add 150 µL/well of Buffer E-H_2O_2 (prepared just prior to pipeting in the microtiter plate wells). The plate is shaken for 20-30 min. at room temperature using an

orbital shaker. Add 50 μL/well of a 2.5N HCl solution. The plate is shaken 3 min. with the orbital shaker at room temperature. The absorbance of the wells is read with a microtiter plate reader at 490 nm. Print the sheet of data and properly label.

Please replace the paragraph at page 209, lines 11-22 with the following paragraph:

Draw Table 19 with a computer. Using the data sheet of the microtiter plate reader, enter the average absorbance values of blanks, controls (no free hapten present), standards and samples in Table 19. Draw the calibration curve on a semi-logarithmic plot (absorbance at 490 nm as a function of the standard concentrations) using sigma-plot (or other plot software). Find the [AAMU] (or [1X]) in the microtiter well of the unknowns from the calibration curve and enter the data in Table 20. Multiply the [caffeine] ([1,7-DMX] or [1,7-DMU] of the unknown by the dilution factor and enter the result in the corresponding cell of Table 20.

Please replace the title of the table at page 210, lines 1 through 2 with the following title:

Table 19

Average absorbance values of samples in the microtiter plate

Please replace the title of the table at page 211, lines 1 through 2 with the following title:

Table 20

Caffeine, 1,7-DMX and 1,7-DMU concentrations in urine samples

Please replace the title of the table at page 212, lines 1 through 2 with the following title:

Table 21

Composition of the different buffers

Please replace the paragraph at page 212, line 5 through page 213, line 5 with the following paragraph:

Accordingly, an ELISA system is provided that is specific for at least NAT2. Alternatively, the ELISA protocol outlined hereinabove, may be adapted for a plurality of enzymes of interest. Fig. 24 exemplifies a multi-determinant assay according to an embodiment of the present invention. Furtherstill, a multi-determinant assay of the present invention may provide more that one 6 X 6 array, as illustrated in Fig. 25, in each well of a standard microplate. Preferably, each well will be provided with 4 6 x 6 arrays according to this aspect of the present invention.

Please replace the paragraph at page 213, lines 6 through 17 with the following paragraph:

The single or multi-determinant assay system of the present invention include(s) metabolite-specific binding agents for the detection of drug-specific metabolites in a biological sample. Such binding agents are preferably antibodies and the assay system is preferably an ELISA, as exemplified in the cases of NAT2 discussed herein above. A detection method according to an embodiment of the present invention is exemplified in Fig. 26. An assay system of the present invention is exemplified in Fig. 27 and provides means to detect metabolites specific to the metabolic pathway(s) used to metabolize amonafide.

Please replace the paragraph at page 216, line 9 through page 217, line 21 with the following paragraph:

The importance of drug metabolism in determining an individual's rate of drug clearance renders it as the most important factor in determining the efficacy and toxicity of many drugs. Some of the metabolic enzymes mentioned in the context of this invention have a clear bimodal distribution of metabolism, allowing the separation of the population into poor and extensive metabolizers. However, within each phenotypic group there is a wide variation in metabolic rates. It may be a naïve to regard all individuals with metabolic ratios greater than a predetermined cut off value as being equivalent. This attempt to classify the population in two or three phenotypic groups is even more difficult for enzymes without a bimodal distribution. The classification of individuals into this limited classification may not allow for the complete exploitation of an individual's pattern of metabolism. In some cases this simple classification is sufficient. For example, some individuals may have an enzyme specific deficiency, such as CYP2D6 and as a result are at risk for severe complications if high doses of a particular drug, such as Prozac™ are prescribed. However, this simple classification would not allow for differential dosing of the extensive metabolizers as a function of the molar ratio calculated during determination of phenotype. If the simple classification of extensive CYP2D6 metabolizers was used, all individuals with a molar ratio of >0.3 (dextromethorphan as probe drug) would receive the same dose. We are proposing the development of a dosing scale that would produce an increasing dose with increasing metabolic ratio, as exemplified in Fig. 28. If only the bimodal distribution is considered, only two possible doses can be prescribed. Accordingly, the individualization of therapy with amonafide is proposed in accordance with the present invention. As a result, the categorical treatment with amonafide

based on phenotype will be replaced with individualization of treatment whereby the metabolism of each individual is assessed on an individual basis and a corresponding individual dosage is determined. In this manner, amonafide is prescribed on an individual basis in dosages corresponding with an individual's phenotypic ability for metabolism.

Please replace the paragraph at page 220, lines 2 through 8 with the following paragraph:

Amonafide has been shown to have antitumor activity in non-small cell lung cancer, prostate cancer and breast cancer. The most common dose-limiting side effect of amonafide has been granulocytopenia. Amonafide is metabolized by NAT2, forming its major metabolite N-acetylamonafide. Fig. 29 depicts the structures of amonafide and N-acetylamonafide.

Replace the paragraph at page 240, lines 1-2 with the following paragraph:

e) karnofsky score ≥70 (Table 22) with an expected survival of 12 weeks;

Replace the title of the table at page 241, lines 20 through 21 with the following title:

Table 22

Karnofsky Performance Scale

Replace the paragraph at page 242, lines 14 through 18 with the following paragraph:

b) unstable angina pectoris, cardiac insufficiency (NYHA Class III-IV; see Table 23), uncontrolled arrhythmia, or uncontrolled hypertension at the time of signature of the consent form;

Replace the title of the table at page 245, lines 1 through 2 with the following title:

Table 23

New York Heart Association (NYHA) Functional Classification

Replace the paragraph at page 249, line 1 with the following paragraph:

7) Karnofsky performance status (see Table 22);

Replace the paragraph at page 249, lines 2 through 3 with the following paragraph:

8) New York Heart Association Classification (NYHA class, see Table 23);

Replace the paragraph at page 252, lines 13 through 14 with the following paragraph:

1) Quality of Life questionnaires EORTC QLQ-C30 and QLQ-BR23 (see Table 24);

Replace the title of the table at page 253, lines 1 and 2 with the following title:

Table 24

EORTC Quality of Life Questionnaire

Replace the paragraph at page 258, line 4 with the following paragraph:

3) Karnofsky performance status (see Table 22);

Replace the paragraph at page 258, line 28 through 259, line 5 with the following paragraph:

Tumor response will be assessed in individuals to define complete response (CR), partial response (PR), stable disease (SD) and disease progression (PD) according to the Response Evaluation Criteria In Solid Tumors (RECIST criteria) as defined in Table 25 In the case of differences in response category between assessments made by the CT-scan and X-ray, the CT-scan will be considered the more accurate technique.

Replace the title of the table at page 260, lines 1 and 2 with the following title:

Table 25

Measurability of Disease and Criteria for Analysis

Replace the paragraph at page 262, lines 26 through 27 with the following paragraph:

1) Quality of Life questionnaires QLQ-C30 and QLQ-BR23 (see Table 24);

Replace the paragraph at page 262, line 30 with the following paragraph:

4) Karnofsky performance status (see Table 22);

Replace the paragraph at page 263, line 28 with the following paragraph:

4) Karnofsky performance status (see Table 22);

Replace the paragraph at page 273 lines 19-23 with the following paragraph:

All doses of amonafide will be calculated on the basis of milligrams of drug per square meter of body surface area as measured at baseline (mg/m^2). A nomogram for the assessment of body surface area from the individual height and weight is given in Fig. 30.

Replace the paragraph at page 277, lines 23 through 27 with the following paragraph:

Following the first treatment cycle of amonafide, each individual will be assessed for signs of adverse events and disease related signs and symptoms according to the NCI-CTG Expanded Common Toxicity Criteria (see Table 26) on Day 12.

Replace the paragraph at page 277, line 28 through page 278, line 2 with the following paragraph:

A65

Each individual will be assessed at the end of each treatment cycle for signs of adverse events and disease related signs and symptoms according to the NCI-CTG Expanded Common Toxicity Criteria (see Table 26).

Replace the title of the table at page 279, lines 1 through 2 with the following title:

A66

Table 26

NCIC-CTG Expanded Common Toxicity Criteria

Replace the paragraph at page 296, lines 5 through 9 with the following paragraph:

A67

The severity of AEs will be assessed according to the NCIC Expanded Common Toxicity Criteria (Table 26). The following definitions should be used for toxicities that are not defined in the NCIC Expanded Common Toxicity Criteria: